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# Thoracic Endometriosis Syndrome

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## Key Words

Hemoptysis · Endometriosis · Pneumothorax · Thoracic endometriosis syndrome

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## Abstract

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity and is usually confined to the pelvis. Thoracic endometriosis syndrome (TES) is a rare disorder characterized by the presence of functioning endometrial tissue in the pleura, the lung parenchyma and the airways. TES may present with hemoptysis, due to the shedding of endometrial tissue in the bronchial tree, or spontaneous pneumothorax or hemothorax if the endometrial tissue is localized peripherally. Patients are of reproductive age, often nulliparous, with long-standing symptoms. The crucial issue for establishing the diagnosis is the cyclicity of the symptoms which occur along with the menstrual cycle. TES is virtually a diagnosis of exclusion, established on clinical grounds, since neither CT nor endoscopy are specific for TES. Treatment consists of gonadotropin-releasing hormone analogues, aiming to suppress the hypophyseal-gonadal axis, so as to ensure a regression of the endometrial implants. If medical treatment fails, surgical resection of the endometriomas is suggested, although relapse rate may be high.

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## Introduction

Endometriosis is defined as the presence of functioning endometrial tissue in extrauterine sites, most commonly the ovaries, the uterosacral ligaments and the cul-de-sac peritoneum. It is a very common disease affecting 5–15% of women during their reproductive years [1]. Less common sites of endometriosis are the uterine tubes, the serosal surface of the uterus, the rectovaginal septum, the sigmoid colon, the pelvic peritoneum and the small intestine. Although endometriosis is usually confined to the pelvis, it may also affect extrapelvic organs. Ectopic endometrium has been found in extrapelvic sites, such as in the umbilicus, in abdominal scars, in the breasts, the extremities, the pleural cavity and the lung [2]. Endometriosis is thought to occur by 1 or more of 3 mechanisms: retrograde regurgitation of endometrium through the oviducts, müllerian metaplasia of coelomic epithelium, and lymphatic and venous dissemination of endometrial tissue to distant sites and implantation. Current investigation focuses on the factors favoring the growth and development of endometrial tissue in the peritoneal cavity in some women and its regression and resorption in others [1, 3]. The clinical presentation of endometriosis is extremely pleiomorphic and thus the diagnosis is difficult. Dysmenorrhea, dyspareunia, chronic abdominal pain and infertility are the most common clinical findings. Extrapelvic or nongynecologic endometriosis has drawn special attention because of the diversity of affected sites and the unusual symptomatology associated with this clinical entity [2]. The location of extrapelvic endo-

metriosis can be divided into 4 anatomic regions: pulmonary endometriosis, bowel-omental endometriosis, urinary tract endometriosis and endometriosis of other sites. Though symptomatology in extrapelvic endometriosis is usually related to the menstrual cycle, this is not the case in all patients, making the diagnosis difficult [4]. The prevalence of extrapelvic endometriosis is unknown because of a lack of epidemiologically well-designed studies. The variety of symptoms, signs and locations and the difficulty in establishing the diagnosis of the disease are the main difficulties in estimating the prevalence of the disease [5]. Extrapelvic endometriosis has many histologic patterns varying from typical endometrial glands to an abundance of fibrous tissue [6].

### Pathogenesis

The respiratory system is the most frequent extrapelvic location of endometriosis [7]. It is a rare disorder characterized by the presence of functional endometrial tissue within the pleura, the lung parenchyma or the airways [8]. In a review of 65 cases of thoracic endometriosis, 54 cases were pleural and only 11 cases were characterized as parenchymal [9]. The tissue is responsive to circulating sex hormones and clinical manifestations are related to the menstrual cycle (catamenial) and are likeliest to occur with menses [7]. The pathogenesis of thoracic endometriosis remains elusive. Two different theories have been proposed. Ivanoff's metaplasia theory postulates that the pleura which develop in the coelomic cavity in utero may undergo metaplasia to form pleural endometrial tissue [8]. A second theory is the retrograde menstruation with transdiaphragmatic passage and subsequent implantation of the stromal and glandular elements of endometrium in the thoracic cavity [8, 9]. This is supported by the surgical findings of associated diaphragmatic endometriosis in the case of pleural endometriosis [10]. The retrograde flow of endometrial tissue through the fallopian tube and its inadequate clearance from the peritoneal cavity are conditions which facilitate the access of endometrial tissue to the thorax, either through congenital defects of the diaphragm (most commonly on the right side) or via embolization through pelvic veins [11]. Beyond the 2 classic theories, a third proposed pathogenetic mechanism involves hematogenic migration following a surgical gynecologic procedure [12]. The parenchymal type of thoracic endometriosis may be best explained by this theory of blood-borne metastases of endometrial tissue, since it is supported by histopatho-

logic findings of endovascular endometrial epithelium in lung biopsies [10].

Thoracic endometriosis is also related to spontaneous pneumothorax which in most cases occurs during menses. Pneumothorax is usually related to the existence of diaphragmatic endometriosis [13]. The frequency of histologically confirmed diaphragmatic endometriosis associated with catamenial pneumothorax varies from 20 to 49% [14]. Clinical and pathologic evidence of pelvic endometriosis was found in 22–37% of patients with catamenial pneumothorax [15]. These diaphragmatic endometrial implants create channels or 'holes' through the diaphragm that will allow further implants to move into the chest or allow the translocation of air [16]. Kirschner [17] introduced the concept of the porous diaphragm syndrome in 1998, proposing the theory that preexisting diaphragmatic defects may allow gas and fluids to traverse this anatomic boundary. During menses the dissolving cervical mucus plug may allow the ascent of air through the fallopian tubes into the abdomen and through diaphragmatic fenestrations into the thorax [18]. Spontaneous postpartum pneumoperitoneum and postcoital pneumothorax have also been reported [19, 20]. The theory of transfallopian ascent of air is supported by the report that plication of diaphragmatic perforations and tubal ligation have cured catamenial pneumothorax [21]. Studies have also documented pneumoperitoneum occurring concomitantly with pneumothorax [22]. Alifano et al. [23], evaluating the incidence of catamenial pneumothorax among women who have been referred for the surgical treatment of spontaneous pneumothorax, showed that catamenial pneumothorax is more frequent than expected and that diaphragmatic abnormalities seem to play a fundamental role in its pathogenesis.

Lillington et al. [24] proposed a second pathogenetic theory for catamenial pneumothorax. They suggested a model in which the expansion of intraparenchymal subpleural endometriotic tissue during menses would cause a check valve airway obstruction, eventually leading to alveolar rupture. High levels of serum prostaglandin causing vasospasm and bronchospasm during menses may also augment alveolar rupture in lung areas with intraparenchymal endometriosis, resulting in pneumothorax [8, 18]. Furthermore, adhesions caused by endometrial tissue involving the pleura, the lung parenchyma or the chest wall create a situation in which minor increases in intrathoracic pressure may create barotrauma. Engorgement of the endometrial tissue during menses makes the risk of pneumothorax highest during this phase of the menstrual cycle [25].

## Clinical Presentation

Thoracic endometriosis has varying clinical presentations. The largest series reviewed 112 cases with a mean age at diagnosis of 35 years (range 19–54 years). Pneumothorax occurred in 73% of the cases, hemothorax in 14%, hemoptysis in 7% and pulmonary nodules in 6%. Patients presented with chest pain in 90% of the cases and with dyspnea in 31%. In 90% of patients, the symptoms occurred within 2 days after the onset of menstruation (table 1). Due to this clinical presentation the term thoracic endometriosis syndrome is proposed (TES). Hemoptysis is a common clinical problem with many potential etiologies which can be caused by a variety of pulmonary diseases, including infections, chronic bronchitis and malignancies [26]. A history of hemoptysis concurrent with menstrual periods helps to differentiate catamenial hemoptysis from hemoptysis of other causes [27–29]. Catamenial pneumothorax is another common presentation of thoracic endometriosis. It manifests as spontaneous pneumothorax and is characterized by chest pain, shortness of breath and absence of respiratory sounds. The symptoms usually develop within 48–72 h of the start of menstrual bleeding. Endometrial implants associated with catamenial pneumothorax are commonly found on the diaphragm at the time of thoracotomy or pleuroscopy. Bleeding and breakdown of pleural endometrial foci during menses could further lead to hemothorax [15]. The majority of pneumothoraces are right sided, although left-sided and bilateral pneumothoraces have been reported [25]. Clinical suspicion and recognition of the temporal relationship of the patient's symptoms with menses is essential to establish the diagnosis [30].

## Diagnosis

The diagnosis of TES is challenging, and it is often delayed until the symptoms' temporal relationship with menses is recognized (table 2). The diagnosis of thoracic endometriosis is therefore made on the basis of the clinical history and is virtually a diagnosis of exclusion [31]. The X-ray in pulmonary endometriosis may reveal pleural effusion or nodular opacities, but often may be normal. Chest computed tomography (CT) findings include opacities, nodular lesions, thin-walled cavities and bullous formations [8]. Chest CT scan or magnetic resonance imaging, however, should be performed during menses for maximal diagnostic sensitivity [32]. In cases

**Table 1.** Symptoms and clinical complications of TES

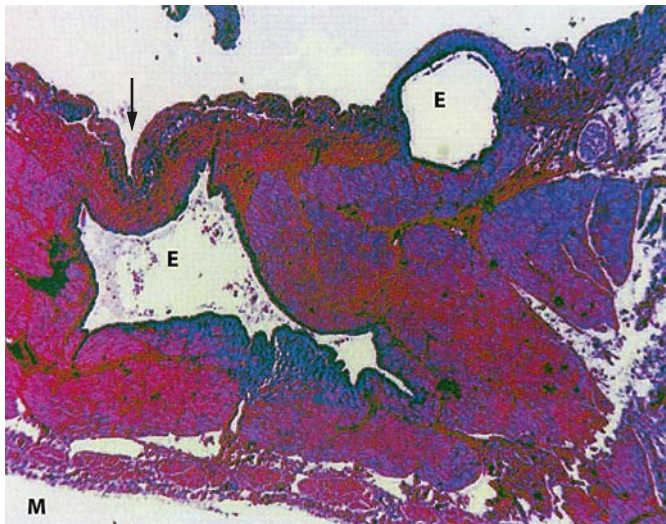
	Frequency %
<i>Symptoms</i>	
Chest pain	90
Dyspnea	31
Cough	rare
Nausea	rare
<i>Clinical complications</i>	
Catamenial pneumothorax	73
Catamenial hemothorax	14
Catamenial hemoptysis	7
Pulmonary nodules	6

**Table 2.** Methods employed in the diagnosis of TES

	Findings
<i>Noninvasive methods</i>	
Chest X-ray	Pleural effusion, opacities, nodular infiltrates
Chest CT scan or MRI	Opacities, nodules, thin-walled cavities, bullous formations; maybe nondiagnostic unless performed during menses
<i>Invasive methods</i>	
Video-assisted thoracoscopy (method of choice)	Diaphragm perforations, nodular or plaque-like, brown or violet endometrial deposits, usually <1 cm in size
Bronchoscopy	In most cases nondiagnostic; may reveal multiple pin-like red submucosal lesions
Bronchial biopsy	Nondiagnostic
Brush cytology	May reveal endometrial cells

of tracheobroncheal endometriosis without parenchymal involvement, chest CT scan is usually nondiagnostic and may reveal only mild thickening of the bronchial wall [33]. Magnetic resonance imaging may be superior to CT in detecting pulmonary endometriosis, while angiography is of little value in establishing the diagnosis [26].

The utility of bronchoscopy is limited, because most cases of TES involve the distal parenchyma. Bronchoscopic examination of the airways often reveals normal findings, but in rare instances endometrial tissue may be seen in endobronchial biopsy [12, 26]. In central airway endometriosis, endoscopic findings at the onset of menses vary from single or scattered purplish-red submucosal patches to white cystic lesions. The lesions disappear after menses,



**Fig. 1.** Endobronchial endometriosis. The patient presented with catamenial hemoptysis and the diagnosis was established with the use of spiral CT. The patient underwent a subsegmentectomy of the upper part of the lateral basal segment. The distal part of the histopathologically examined resected specimen is presented. To the right of the arrow, ciliated columnar epithelium has been replaced by endometrium, although the smooth muscle layer has been retained. Hemosiderosis can be seen in the lung parenchyma. Hematoxylin-eosin.  $\times 40$ . Reproduced with permission from Terada et al. [9].

and a crypt can be observed as a sign of the cysts' healing. Surgery is frequently needed to establish the diagnosis, and more than 60% of affected patients require thoracotomy or thoracoscopy as part of the diagnostic approach [8]. Histopathologic confirmation of pulmonary endometriosis is also difficult since both biopsy and resected specimens should be obtained just before the onset of menses [34]. Histopathologic diagnosis has been obtained in only one third of the cases reported in the literature (fig. 1) [34, 35]. Pleural fluid cytologic examination is rarely helpful. Concluding, the main criterion for the diagnosis is the finding of periodic symptomatology that is synchronous with menstruation. Most of the reported cases were diagnosed on the basis of the patient's clinical history, without a supportive histologic confirmation (table 3) [35].

### Treatment

The pharmacologic inhibition of sex hormones with gonadotropin-releasing hormone (GnRH) analogues is the treatment of choice for pulmonary endometriosis, since these drugs are reported to have the same efficacy

**Table 3.** Differential diagnosis of TES with other pulmonary diseases

Symptom	Key diagnostic features
Chest pain	Mild to moderate Right sided Frequently coexisting with shoulder pain Cyclic in nature, occurring within 72 h from onset of menses Almost always related to pneumothorax or hemothorax
Cough, shortness of breath	Cyclic in nature, usually within 72 h from onset of menses
Hemoptysis	Cyclic in nature, occurs during menses

as in the case of pelvic endometriosis [12, 23, 36]. Medical treatment is expensive, and the symptoms often recur after it is discontinued. Furthermore, since these drugs inhibit ovulation, patients who wish to conceive sometimes refuse to undergo hormone therapy [34, 36]. Older therapies consist of the suppression of endometrial tissue with danazol or progesterone, promoting a pseudopregnancy status [37]. The indications for pulmonary surgery are hormonal therapy failure, intolerable adverse effects or symptom recurrence after cessation of medical treatment. The longest reported follow-up periods have been 10 months after surgical treatment and 12 months after treatment with danazol and buserelin. Pleural manifestations, however, are often difficult to treat surgically because the lesions tend to be multifocal. Therefore, a single focus of bleeding must be conclusively located before surgery. When the lesions are multiple or when their location cannot be detected, oophorectomy may be considered if fertility is not an issue [12]. On the other hand, surgery should be the preferred method if the patient wishes to become pregnant. For peripheral lesions, video-assisted thoracoscopic wedge resections have been successfully performed and this is considered as the preferred method of surgical treatment. In patients with centrally located bronchial endometriosis, subsegmentectomy, segmentectomy or lobectomy may be required [34, 38]. In a review of 229 cases of catamenial pneumothorax, adequate work-up was available for 195 patients (85.2%). One hundred fifty-four (79%) were treated surgically, with detailed pathologic findings reported for 140 (91%), and 54 (38.8%) showed diaphragmatic lesions. Pleurodesis, with or without diaphragmatic repair or wedge resection, was performed in 82% of the cases [39].

**Table 4.** Case reports of thoracic endometriosis

Reference	Age	Clinical presentation	Diagnosis	Treatment
Roberts et al., 2003 [18]	28	Catamenial pneumothorax, chest pain, constipation, bloody stools	Thoracoscopy	Surgical removal of pleural endometriomas, low anterior rectal resection
Yu et al., 2002 [26]	32	Catamenial hemoptysis	CT	Oral contraceptives
Ziedalski et al., 2004 [8]	28	Catamenial pneumothorax, cough, dyspnea, chest pain	Pleural fluid cytology	Lobectomy
Hong et al., 1999 [10]	23	Catamenial hemoptysis	CT	Lobectomy
Matalliotakis et al., 2002 [5]	29	Catamenial hemoptysis	MRI	GnRH analogues
Terada et al., 1999 [9]	29	Catamenial hemoptysis	CT	Subsegmentectomy
Ghio et al., 1988 [15]	39	Catamenial pneumothorax, chest pain	Chest radiography	Medroxyprogesterone acetate

### Case Reports of Thoracic Endometriosis

Ghio et al. [15] reported a case of a patient with catamenial pneumothorax, shortness of breath, cough and chest pain in whom pneumothoraces developed between menses as well as in the beginning. Chest radiographs showed small right-sided pneumothorax. The diagnosis of TES was established on clinical grounds, and oral contraceptives were started, which, however, failed to control her pain. Treatment with medroxyprogesterone acetate resulted in long-lasting remission. As the authors suggested, the midcycle pneumothorax may have resulted from imperfect regeneration of endometrial tissue in a subpleural location with scarring and possible pleural traction (table 4).

Ziedalski et al. [8] reported a case of a young woman with multiple hospitalizations during the previous 3 years for right-sided pneumothorax and hemothorax 24 h after the onset of menses. The patient underwent thoracocentesis and the cytologic examination demonstrated endometrial epithelial cells with no evidence of malignancy. The patient underwent pleurectomy, with removal of the pleural implant. One year later, she was free of symptoms.

Roberts et al. [18] reported a case of recurrent catamenial pneumothorax and diaphragmatic endometriosis which presented with chest pain, shortness of breath, bloody stools and chronic constipation in a woman with a history of pelvic endometriosis. A preoperative chest X-ray revealed a right pneumothorax. Colonoscopy revealed biopsy-proven endometriosis of the sigmoid colon. The patient underwent laparoscopic excision of her pelvic endometriomas, including a low anterior rectal resection. A thoracoscopic right total pleurectomy was performed

for recurrent pneumothorax. This case emphasizes the importance of a careful review of systems in patients with known endometriosis.

Yu et al. [26] reported a case of pulmonary endometriosis presenting with catamenial hemoptysis, mild anemia and normal X-ray. CT of the chest revealed ill-defined infiltrate in the left upper lobe posterior segment and pelvic ultrasound revealed no evidence of endometriosis. The patient was treated with oral contraceptives for 2 months and hemoptysis did not recur during 18 months of follow-up.

Matalliotakis et al. [5] recently reported a case of catamenial hemoptysis, secondary infertility, and pelvic endometriosis associated with a unicornuate uterus and a noncommunicating rudimentary horn. Diagnostic laparoscopy revealed stage III endometriosis involving the right ovary and cul-de-sac. She was successfully treated with GnRH agonists for 6 months, but the symptoms reappeared after cessation of treatment. After a second 6-month trial with GnRH agonists the patient became pregnant and the rudimentary uterine horn was removed during cesarean section. The patient remained asymptomatic thereafter.

Hong et al. [10] reported a case of recurrent episodes of hemoptysis simultaneously with the beginning of menstruation. Computed tomography of the chest disclosed a well-demarcated area of opacity suggestive of parenchymal hemorrhage and histopathologic examination of the resected specimen revealed pulmonary endometriosis. She underwent basal segmental resection of the right lower lobe with no recurrence of hemoptysis during 3 months of follow-up in the outpatient clinic.

Terada et al. [9] presented a case of a 29-year-old woman with a 1-year history of recurrent hemoptysis. A solid solitary subpleural lesion was diagnosed by spiral CT. The patient underwent subsegmentectomy and histopathologic examination revealed findings typical of endobronchial endometriosis. Postsurgically, the patient has been asymptomatic for 11 months with no recurrence of hemoptysis.

## Conclusions

The symptoms and complaints associated with thoracic endometriosis are quite diverse and usually relate to the physiologic function of the ectopic endometrial site.

Thoracic endometriosis may be suspected in women of reproductive age with spontaneous recurrent pneumothorax or hemoptysis, even in the absence of symptoms associated with pelvic endometriosis. The diagnosis of thoracic endometriosis is usually based on clinical symptoms, since localization procedures including endoscopy are in many cases nondiagnostic. Medical treatment consists of GnRH analogues. Surgical treatment is employed in cases of medical treatment failure or recurrence after cessation of treatment. Bilateral oophorectomy may be considered if pulmonary involvement is multifocal or unresectable. A high index of suspicion is required in order to recognize and promptly treat this rare clinical entity.

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